Steroid reversibility test followed by inhaled budesonide or placebo in outpatients with stable chronic obstructive pulmonary disease

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The aim of this study was to evaluate the predictive value of a 2-week course of prednisolone on the effect of 6-months treatment with inhaled budesonide in patients with stable chronic obstructive pulmonary disease (COPD). Forty patients with stable COPD entered the study, and received prednisolone (37.5 mg o.d.) for 2 weeks. They were subsequently divided into steroid-irreversible and steroid-reversible, using 15% of baseline as a dividing point. In each group patients were randomized to receive budesonide 400 µg b.i.d. or placebo for 6 months. During treatment with prednisolone, three patients dropped out because of side effects. Of the remaining 37, only two patients (5%) were reversible with prednisolone (forced expiratory volume in 1s [FEV1] > 15% of baseline), and among the steroid-irreversible, 26 patients were evaluated after 6 months treatment with either placebo or budesonide. No significant differences in spirometry values, symptoms, or number of exacerbations were found between these two groups. Reversibility with prednisolone is rarely seen in COPD. In outpatients with stable COPD and no signs of asthma or atopy, 2 weeks treatment with prednisolone seems to be of no value in choosing subsequent long-term therapy.

Introduction

The use of corticosteroids is a well-established part of treatment for asthma (1,2), whereas their use in chronic obstructive pulmonary disease (COPD) is still debated (3,4). Inflammation in asthma, and COPD is distinctly different and therefore corticosteroids would be expected to be less effective in this latter disease.

For many years, the use of treatment with systemic corticosteroids of short-duration has been one of the methods that distinguished asthma from COPD, and was a method used to select patients with COPD, who would probably benefit from long-term treatment with inhaled corticosteroids (5,6). The short duration oral steroid test is frequently used to ascertain if there is an asthmatic component in the disease.

Several randomized, placebo-controlled, double-blind clinical trials have evaluated systemic corticosteroids in stable COPD, but with a wide variation in design and quality (7). A recent meta-analysis of 10 randomized, double-blind placebo-controlled trials with well-defined exclusion criteria (no asthmatics included) concluded that subjects who received corticosteroid treatment were approximately 10% more likely to experience an increase 20% or more in the baseline FEV1 compared with those who received placebo (8). Only one of these 10 studies lasted 2 weeks. The average prednisolone dose was 35–40 mg daily.

The clinical implication of a significant increase in FEV1 during 1–2 weeks of prednisolone treatment is still debated. No controlled trials have shown that these 'steroid-reversible' COPD patients gain any benefit from long-term treatment with either systemic or inhaled corticosteroids on FEV1 decline. The aim of this study was to evaluate the predictive value of a 2-week course of prednisolone on the effect of 6 months treatment with inhaled budesonide in patients with stable COPD.

Material and methods

This study was a placebo-controlled, randomized, double-blind multicentre trial, conducted at five centres in Denmark. Standard spirometry (Vitalograph™️) was performed on possible study subjects before the start of the study. Outpatients aged 18–75 years with stable COPD were
Included. Stable COPD was defined as a FEV₁, forced vital capacity (FVC) < 0.7, a post-bronchodilator FEV₁ <70% of predicted, FEV₁ >40% of predicted and an increase in FEV₁ <15% after inhalation of 0.5 mg terbutaline, via a dry powder inhaler (Bricanyl Turbuhaler™). At the first visit, a blood sample was drawn for analysis of eosinophil count and total blood IgE concentration (the latter quantitated by an immunological reaction in which specific rabbit anti-IgE antibodies react with human IgE-antigen). The exclusion criteria were clinical evidence of asthma (e.g. pollen season related symptoms, exercise-induced symptoms only and significantly elevated levels of eosinophils and IgE), a history of atopy (hay fever and/or atopic dermatitis), treatment with inhaled corticosteroids within the last 6 months, treatment with oral corticosteroids, chromoglycate or nedocromil within the last 4 weeks, other systemic disease making compliance and participation in the study difficult, pregnancy and breast feeding, and an increase in FEV₁ >30% of baseline after 2 weeks of prednisolone treatment.

All patients received 2 weeks treatment with oral prednisolone 37.5 mg daily. Reversible patients with 15% <ΔFEV₁ <30% of baseline and irreversible patients with ΔFEV₁ <15% were separately randomized to either inhaled budesonide 400 μg b.i.d. or placebo (Spirocort™ Turbuhaler™, Astra Danmark A/S). Spirometric values, number of exacerbations, symptom score and adverse events were recorded at monthly visits at the respiratory outpatient clinics. All patients gave written informed consent. The study was approved by the local ethics committees and conducted in accordance with the declaration of Helsinki.

The primary effect parameter was a change in FEV₁, and for a study power of 90%; a total of 120 patients were needed to detect a difference of 100 ml at the 5% significance level.

Non-parametric statistical methods (Mann-Whitney U-test) were used, as data were not normally distributed.

**Results**

A total of 40 patients were included in the study. Median FEV₁ was 1.49 l (range 0.8–2.45 l). None of the patients had clinical evident asthma, atopy or elevated eosinophils/IgE. All were irreversible (ΔFEV₁ <15% of baseline) with the inhaled β₂-agonist. All but one were either smokers or ex-smokers, the exception being a woman married to a heavy smoker. The flow of evaluable patients and drop-outs is schematically shown in Fig. 1.

All patients started treatment with prednisolone, but three patients were withdrawn because of side effects caused by prednisolone (restlessness and insomnia). Of the 37 patients who completed 2 weeks prednisolone treatment, only two patients (5%) were found to be reversible (ΔFEV₁ >15% of baseline). During the subsequent 6 months treatment with budesonide or placebo, one of the patients in the 'reversibility' group dropped out without explanation, and thus only one patient completed 6 months of treatment. Because of the very low number of patients in this treatment arm, further statistical analysis comparing steroid-irreversible with steroid-reversible patients would be meaningless.

In the steroid-irreversible group, 14 patients were randomized to budesonide and 12 patients received placebo. There were no significant differences between the two groups in demographic data, baseline spirometric values, or smoking history. In the budesonide group, eight were males (57%), median age was 58.5 years (range 51–74 years), and the median FEV₁ was 1.46 l (range 0.9–2.6 l). In the placebo group, six were males (50%), the median age was 62.5 years (range 57–74 years) and median FEV₁ was 1.63 l (range 0.8–2.45 l).

After 6 months of treatment, the median decrease in post-bronchodilator FEV₁ in the budesonide group was 0.021 l (range 0.25–0.23 l) compared to a median decrease of 0.125 l (range 0.7–0.23 l) in the placebo group, P=0.106 (Mann–Whitney U-test). There was no difference in the number of exacerbations, adverse events or symptom scores between the active and the placebo group (P>0.4, Mann–Whitney U-test).

**Discussion**

In this multicentre study only 40 patients were included, a number well below the calculated sample size. We found only two patients (5%) with an increase in FEV₁ >15% of baseline after 2 weeks of treatment with prednisolone. Furthermore, none of our patients were reversible to an inhaled β₂-agonist. Thus, in our patients, who were carefully selected to be non-asthmatics without temporary worsening of their pulmonary disease, 2 weeks treatment...
with systemic corticosteroids did not increase the spirometric values, nor did it improve the symptom score or the number of exacerbations. Thus, we were unable to carry out the study as originally planned.

Some benefits have been reported from short-term use of inhaled corticosteroids (9,10), although their use in steroid-irreversible patients has recently been questioned (11). In a 2 year study with high-dose inhaled corticosteroids, Renkema et al. showed some improvement in symptoms, but not in lung function among 47 COPD patients (12). Results from large scale, long-term studies with inhaled corticosteroids are still awaited (13). Preliminary results from EUROSCOP, ISOI DF and the Copenhagen Lung Study have been presented in abstract form. In EUROSCOP (budesonide 400 μg b.i.d. vs. placebo for 3 years), a significant effect on FEV₁ was seen within the first 6 months, after which no significant difference in FEV₁ decline was observed. In the ISOLDE study (Fluticasone propionate 500 μg b.i.d. vs. placebo for 3 years), the same pattern was seen, although a beneficial effect on exacerbation rate and quality of life parameters was observed. In the Copenhagen Lung Study, no difference between placebo and steroid-groups was observed; 290 patients were treated with either placebo or budesonide 800+400 μg daily during the first 6 months followed by either placebo or budesonide 400 μg b.i.d. for 2.5 years. Furthermore, there seem to be different opinions on how to define reversibility in COPD patients (14-17), and finally some authors believe that a few weeks’ treatment with corticosteroids is not enough time to detect steroid-responders (18). From treatment with bronchodilators it is also known whether the result of a short-term reversibility test necessarily correlates well with the patients’ self-assessment after long-term treatment (19).

All patients in this study had a decrease in FEV₁ during the 6 months of treatment with either budesonide or placebo. The placebo group showed a greater decrease in FEV₁, but there was no significant difference between the groups. Our findings could indicate a beneficial effect of inhaled budesonide in patients with stable COPD, but the results from large-scale long-term studies in prednisolone-irreversible COPD patients are needed before any conclusions can be made.

We conclude that in patients with stable COPD (as judged by medical history and careful spirometric evaluation with a reversibility test to a bronchodilator), and no history or signs of asthma or other atopic disease, there is no reason to conduct short-term treatment with corticosteroids in order to evaluate any possible reversibility.

References


